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## SHORT COMMUNICATION

### **The use of midazolam in combination with medetomidine for premedication in healthy dogs**

#### **Abstract**

**Objective** To assess the sedative effects, propofol sparing properties and impact on quality of induction and intubation of intravenous (IV) medetomidine and midazolam administered consecutively at different doses compared to medetomidine alone in healthy dogs for premedication.

**Study design** Prospective, randomized, blinded, clinical study.

**Animals** A total of 40 adult healthy client owned dogs, weighing  $18 \pm 7$  kg (mean  $\pm$  standard deviation).

**Methods** Dogs were assigned to four groups: medetomidine  $15 \mu\text{g kg}^{-1}$  (positive control group), medetomidine  $10 \mu\text{g kg}^{-1}$  & midazolam  $0.2 \text{ mg kg}^{-1}$ , medetomidine  $5 \mu\text{g kg}^{-1}$  & midazolam  $0.3 \text{ mg kg}^{-1}$  and medetomidine  $5 \mu\text{g kg}^{-1}$  & midazolam  $0.2 \mu\text{g kg}^{-1}$ . The same clinician assessed sedation after administration at T2.5 minutes and T5 minutes using a composite simple descriptive sedation scale (CSDS) between 0 and 15 (0= no sedation; 15=profound sedation). The dose of propofol for induction, quality of induction, ease of intubation and any adverse events were recorded.

**Results** There was no significant difference in sedation scores between treatment groups at T2.5 minutes or T5 minutes ( $p=0.82$  and  $p=0.63$  respectively). Administration of midazolam in combination with medetomidine resulted in 71% of dogs displaying paradoxical behaviours ( $p<0.0001$ ) such as agitation, excitation, restlessness, aggression and vocalization which was different from pre-sedation. Propofol requirement was not

different between groups. Induction and tracheal intubation quality was smooth in all groups.

**Conclusion** In healthy dogs, at the doses studied, the combination of medetomidine-midazolam administered IV for premedication provided moderate sedation but was associated with a high incidence of paradoxical behaviours. This drug combination IV is not recommended for premedication in healthy dogs.

**Keywords** Premedication; Sedation; Dog; Midazolam; Medetomidine

## **Introduction**

In veterinary medicine, the number of dogs and cats premedicated before general anaesthesia (GA) is reported to be rising to 100% (Brodelt 2006). It has an important impact on the GA and decreases odd-ratios of anaesthetic deaths and complications (Brodelt 2006). Furthermore, induction is smoother, faster and less induction agent is needed, minimizing side effects (Murrell 2016).

Medetomidine combinations, although not as widely used as acepromazine combinations, are the second most common premedication agents in the UK (Brodelt 2006). Medetomidine provides reliable and profound sedation with a significant drug sparing effect on anaesthetic induction and maintenance agents (Murrell 2016). Midazolam is a commonly used benzodiazepine agent for sedation and premedication in human medicine; providing propofol sparing effects and improving intubation quality (National Institute for Health and Care Excellence 2014). Alone, in healthy dogs it provides minimal sedation (Court & Greenblatt 1992). The combination has been described in a few experimental studies in dogs that suggest improved sedation and a decrease in propofol requirements compared to medetomidine alone (Hayashi et al. 1994; Canfrán et al. 2016).

The aim of this study was to investigate the sedative effects, propofol sparing potential and effect on induction and intubation quality of the combination medetomidine-midazolam compared to medetomidine alone administered IV as premedication prior to GA in healthy dogs.

## **Materials and methods**

### *Animals*

The study protocol was approved by the University Animal Ethical Review Committee (VIN/15/033) and informed owner consent was obtained for all dogs enrolled in the study. The study was also conducted under an Animal Test Certificate (42273/003) and complied with Good Clinical Practice standards. A total of 40 client-owned dogs presenting for elective neutering at a practice were recruited. All animals were healthy based on full clinical examination, were classified as American Society of Anesthesiologists (ASA) I or II, had no or mild pain at presentation and weighed between 10 and 40 kg. Exclusion criteria were dogs not healthy on clinical exam, previous sedation or GA in the last 48 hours or IV catheter placement was not possible whilst conscious. One investigator collected all the data, received training for the sedation scoring system and was unaware of treatment allocation.

#### *Study design and treatments*

Administration of the premedication combinations was pseudorandomised depending on body weight [10-25 kg (SSMALL) and 26-40 kg (SLARGE)] into four groups: medetomidine 15  $\mu\text{g kg}^{-1}$  [Med15 (positive control)], medetomidine 10  $\mu\text{g kg}^{-1}$  & midazolam 0.2  $\text{mg kg}^{-1}$  (Med10mid0.2), medetomidine 5  $\mu\text{g kg}^{-1}$  & midazolam 0.3  $\text{mg kg}^{-1}$  (Med5mid0.3) and medetomidine 5  $\mu\text{g kg}^{-1}$  & midazolam 0.2  $\text{mg kg}^{-1}$  (Med5mid0.2). The treatment administrator was a registered veterinary nurse who was not involved in data collection.

All drugs, medetomidine (1  $\text{mg mL}^{-1}$ , Sedastart; Animal Care Limited) and midazolam (5  $\text{mg mL}^{-1}$ , Dormazepam, Regivet BV) were administered intravenously (IV) over 60 seconds via a preplaced intravenous catheter in separate syringes and flushed with 1 mL of heparin saline (5 IU  $\text{mL}^{-1}$ ) in between. The medetomidine was always administered first followed immediately by midazolam.

## *Experimental protocol*

Once admitted, baseline vital parameters and sedation score were recorded. An intravenous catheter was placed. The investigator was unaware of the treatment allocation and did not observe the preparation and administration of the test drugs. The investigator returned to the induction area to observe the dog immediately after the test drug administration to allow scoring of sedation before induction of anaesthesia using a composite simple descriptive scale (CSDS) ranging from 0 (no sedation) to (15) profound sedation (Appendix A). The time of test drug administration was Time 0 (T=0); sedation were scored again at T2.5 minutes and T5 minutes. Any adverse events during the premedication period were recorded.

The investigator induced anaesthesia five minutes after the test drug administration. Propofol was administered slowly IV to effect in 0.5 mg kg<sup>-1</sup> aliquots and after each dose, depth of anaesthesia was assessed by checking for presence or absence of a palpebral reflex and assessment of jaw tone. Tracheal intubation was attempted when there was loss of a palpebral reflex and the jaw tone was relaxed. The dose of propofol required to allow successful intubation was recorded. Quality of induction and quality of intubation was scored using a simple descriptive scale ranging from 0 to 3 (Appendix B).

Immediately after induction of anaesthesia and tracheal intubation, the endotracheal tube was connected to the circle breathing system and the cuff was inflated to effect until there was no audible leak when the reservoir bag was squeezed. The anaesthetic machine delivered isoflurane vaporised at 2% in 100% oxygen and methadone 0.2 mg kg<sup>-1</sup> was administered IV. The rest of the GA was monitored and performed as normal.

## *Statistics*

A power calculation to determine sample size was based on the study by Raszplewicz et al. (2013) using the same composite sedation scoring system. They indicated that 17 dogs per

group were needed for a statistical power of 90% to detect a difference in sedation scores of 25% with an alpha error of 0.05. Therefore, it was decided to recruit 20 dogs per group in the present investigation. Because of the important number of side effects observed, the study was terminated at 40 dogs instead of 80.

Data were assessed for normality and homogeneity of variance with the appropriate statistical tools. Appropriate tests for parametric and non-parametric data were chosen and data were analysed using SPSS 18 (IBM, NY). One way ANOVA between groups was used to compare body weight, sedation score at T2.5 minutes and T5 minutes, and dose of induction agent. The assumptions of 'normality of errors' and 'homogeneity of variance' were met. Quality of induction and intubation were assessed using a Kruskal Wallis analysis of variance.

A Chi-square test was used to compare the number of dogs per treatment group, signs of paradoxical behaviour at premedication and side effects. When post-hoc testing was carried out, the  $p$  value at 0.05 was adjusted by Bonferroni correction  $p/n$ .

## **Results**

Only 40 dogs were recruited for the study; because of ethical reasons the study was terminated early. This caused the treatment groups to be unbalanced with 12 dogs in groups med15, 9 in group med10mid0.2, 10 in group med5mid0.3 and 9 in group med5mid0.2. There were no significant differences in age ( $p= 0.95$ ) or body weight ( $p=0.74$ ) between the treatment groups.

The sedation score increased over time after treatment administration in all the groups ( $p<0.005$ ). There was not an effect of treatment group on sedation scores over time ( $p=0.84$ ). When compared at individual time points at T2.5 and T5, there was not a difference between treatment groups ( $p=0.82$ ) ( $p=0.63$ ). Similarly, there were no differences in the dose of

propofol ( $\text{mg kg}^{-1}$ ) required for induction ( $p=0.31$ ) (Table 1), the quality of induction ( $p=0.3$ ) or the quality of tracheal intubation between treatment groups ( $p=0.8$ ).

After administration of the test drug(s), some dogs showed signs of agitation, excitation, significant hypersensitivity to noise, restlessness, abnormal change in behaviour, aggression and vocalization defined as paradoxical behaviour, which was significantly different from the pre-sedation state. Dogs premedicated with midazolam (groups med10mid0.2, med5mid0.3, med5mid0.2) were significantly more likely to have paradoxical behaviours, 71 % of cases administered midazolam had paradoxical behaviours ( $p<0.0001$ ) (Table 1).

## Discussion

This study found that consecutive administration of medetomidine and midazolam to healthy dogs provided moderate sedation with severe paradoxical behaviours.

The similar sedation scores between treatments may be associated with the profound effect of medetomidine so that midazolam may not have a significant additive effect when combined with medetomidine (Canfràn et al. (2016). While midazolam in human medicine produces sedation, given alone to healthy dogs, it is associated with paradoxical behaviours (Covey-Crump & Murison 2008; Sanchez et al. 2013). Sanchez et al. (2013), in sedated dogs, found that the administration of midazolam  $0.2 \text{ mg kg}^{-1}$  IV resulted in either no change in degree of sedation or mild to moderate excitement (Sanchez et al. 2013). Covey-Crump and Murison (2008) also suggested that dogs already sedated became 'less sedated' and excited after administration of midazolam  $0.2 \text{ mg kg}^{-1}$  IV as a co-induction agent (Covey-Crump & Murison 2008).

Our findings strongly support previous reports of paradoxical behaviours associated with midazolam administration to healthy dogs. This is characterised by restlessness,



vocalisation and hyper-responsiveness to sound and aggression. In this study 20 out of 28 dogs that received midazolam, displayed excitatory signs after IV administration.

Comparatively to other drugs,  $\alpha_2$ -agonists are the most potent sedatives in veterinary medicine. At normal clinical doses medetomidine is an effective and potent sedative. Consequently, the frequency of excitement associated with the combination of midazolam and medetomidine was unexpected in the study. The pharmacokinetics of medetomidine and midazolam may be responsible. While medetomidine IV at  $40 \mu\text{g kg}^{-1}$ , reaches peak plasma concentrations between 10-15 minutes, midazolam IV takes less than 3 minutes (Court & Greenblatt 1992; Kuusela et al. 2000).

Quality of tracheal intubation was no different between treatment groups. It was hypothesised that dogs premedicated with midazolam and medetomidine would have better quality intubation compared with medetomidine alone. Previous studies have recorded a smoother intubation after administration of midazolam, believed to be associated with its effects on upper airway reflexes (Covey-Crump & Murison 2008). Within the veterinary literature, medetomidine is described as providing smooth conditions for intubation, although there are no previous reports assessing quality with a numerical descriptive scale, similar to our study. In human medicine, the addition of dexmedetomidine to midazolam showed more smooth intubation compared to midazolam alone (Bergese et al. 2010).

The quality of induction was generally smooth and was similar between treatments. Medetomidine as premedication provides good quality induction without excitement (Murrell 2016). On the other hand, midazolam, given prior to propofol in mildly sedated dogs, has been reported to be associated with a lower quality induction (Covey-Crump & Murison 2008). Our results suggest that the combination of medetomidine-midazolam provides smooth induction. This is most probably associated with the prevailing effect of medetomidine.

100           This clinical study had several limitations. First, the number of dogs recruited was not  
101 equal to the number initially calculated in the power analysis. Based on previous reports, to  
102 detect a 25% difference in sedation scores, 17 dogs per treatment group were needed  
103 (Raszplewicz et al. 2013). We recruited only 40 dogs, so the study is underpowered for the  
104 primary outcome. Nevertheless, from the results of the sedation score at T5, with a *p* value of  
105 0.6, it is unlikely that a true effect would have been detected with more dogs. The high  
106 incidence of paradoxical behaviours associated with midazolam administration was an ethical  
107 reason to stop the study. However it also may have biased the assessment outcome because,  
108 although the assessor was blinded to the treatment allocation, the typical behaviours were  
109 obvious. Any analytical techniques, to correct these limitation and solutions, such as  
110 involving a second assessor, would have been impractical and would have inevitably  
111 increased variability in the outcome measures.

## 113 **Conclusions**

114 In healthy dogs, medetomidine and midazolam given consecutively IV does not provide  
115 reliable sedation and is associated with severe behavioural changes. Ease of intubation and  
116 induction were not improved and the results do not suggest that it reduced propofol  
117 requirements.

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